REMARKS/ARGUMENTS

Upon entry of the present amendment, claims 1-14, 16-28 and 55-59 will be pending in this application and presented for examination. The Examiner has indicated that claims 18-28 are allowable. In addition, claim 56 contains allowable subject matter. Claims 2-4, 7-9, 12, 14, 16-17 and 58 are free of the prior art. Claims 1 and 58 have been amended. Claim 60 has been canceled with out prejudice. Reconsideration is respectfully requested.

I. REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 1-14, 16, 17, 58 and 60 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. To the extent the rejections are applicable to the amended set of claims, Applicant respectfully traverses the rejection.

In paragraph A, the Examiner alleges that claims 1-14 and 16-17 are indefinite as the intact NP probe is referred to as an intact NP probe even after enzymatic cleavage.

In response, Applicant has amended claim 1 to recite that "applying an energy field to said sample, thereby separating said phosphate detectable moiety from said sample having an intact NP probe." With the foregoing amendment to the base claim, a skilled person will realize that the sample comprises an intact NP probe with a detectable moiety attached thereto. After enzymatic cleavage, the phosphate detectable moiety will be separated from the sample which comprises additional intact NP probes (please see figure 7). As such, in view of the foregoing amendment, Applicant respectfully requests that the Examiner withdraw the rejection.

In paragraph B, the Examiner alleges that claim 58 is indefinite as the language "said phosphate fluorophore moieties is a used for a member" is apparently unclear.

In response, Applicant has amended claim 58 to recite "said phosphate fluorophore moiety is a used in a sequencing method consisting..". Applicant believes such language is now clear and definite. In this regard, the Examiner is respectfully directed to page 23, lines 25-29. As such, in view of the foregoing amendment, Applicant respectfully requests that the Examiner withdraw the rejection.

In paragraph C, the Examiner alleges that the language of claim 60 is indefinite. In response, Applicant has canceled claim 60 without prejudice, thereby rendering this rejection moot.

In view of the foregoing amendments and cancellation of claim 60, Applicant respectfully requests that the Examiner withdraw the rejection.

II. REJECTION UNDER 35 U.S.C. § 102

Claims 1, 5, 6, 10, 11, 13, 55, 59 and 60 have been rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Hyman (*Anal. Bioch.*, vol. 174, pp. 423-436, 1988). The Examiner alleges that Hyman teaches providing a solution comprising one of four dNTPs and pumping such solution through a column containing an immobilized template-primer-DNA polymerase complex. The Examiner admits that Hyman does not specifically teach that the pyrophosphate moieties carries a molecular charge which is different than the molecular charge of the intact dNTP. To the extent the rejection is applicable to the amended set of claims, Applicant respectfully traverses the rejection.

> MPEP §2131 sets forth: A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Claim 1 has been amended to set forth:

> 1. (Currently Amended) A method for separating an intact NP probe from a phosphate detectable moiety, said method comprising:
> a) providing a sample comprising an intact NP probe with a detectable moiety attached thereto, whereupon an enzymatic cleavage of said intact NP probe to incorporate said NP probe on a primer strand hybridized to a target nucleic acid, a phosphate detectable moiety is produced, wherein said phosphate detectable moiety carries a molecular charge which is different than the molecular charge of said intact NP probe; and

b) applying an energy field to said sample, thereby separating said phosphate detectable moiety from said sample having an intact NP probe.

As amended, present claim 1 recites i) whereupon an enzymatic cleavage of said intact NP probe to incorporate said NP probe on a primer strand hybridized to a target nucleic acid, ii) a phosphate detectable moiety is produced, wherein said phosphate detectable moiety carries a molecular charge which is different than the molecular charge of said intact NP probe; iii) applying an energy field to said sample, thereby separating said phosphate detectable moiety from the sample having an intact NP probe. For example, in Figure 7 of the application as filed, the enzymatic cleavage incorporates the NP probe as well as producing a phosphate detectable moiety. The energy field then separates the phosphate detectable moiety (76) from the sample. The sample comprises an intact NP probe with a detectable moiety attached thereto (77).

In the Hyman method, DNA and DNA polymerase are held by a DEAE-Sepharose column and solutions containing different dNTPs are pumped through. The pyrophosphate that is generated is measured continuously by a device consisting of a series of columns containing enzymes covalently attached to Sepharose. (see, Abstract). As shown on page 424 of Hyman, the PPi generated from the polymerase reaction is used in a sulfurylase-Sepharose column. This enzyme catalyzes the reaction wherein PPi and adenosine 5'-phosphosulfate generate ATP. (please see the top of page 424). The ATP formed in this reaction along with luciferin pass into the luciferase-Sepharose column which generates light. The light emitted is detected by a photomultiplier tube.

Hyman teaches on page 423, column 2, last 6 lines, i) that after the polymerase reaction, ii) the mixture of APS, glucose, glycerol, luciferin, dNTP and PPi then pass through a column of glycerokinase-Sepharose and hexokinase-Sepharose. These kinases selectively break down dATP to dADP (if dATP is chosen) and contaminating ATP to ADP; iii) PPi, APS and luciferin are unaffected by the kinases and enter the sulfurlase-Sepharose column. The ATP formed with luciferin passes into the luciferase column to generate light. (page 424, column 2).

Applicant teaches and claims "b) applying an energy field to said sample, thereby separating said phosphate detectable moiety from said sample". The energy field is used to separate the phosphate detectable moiety from the sample comprising an intact NP probe.

In stark contrast, Hyman teaches the use of an econocolumn pump used in the construction of a flow cell. The flow cell device consists of two needles that penetrate a hallowed out rubber stopper. The one end of the first needle is connected to the pump. The second needle is connected to the waste reservoir. The other ends of the needles are connected to both ends of the luciferase column which is then enclosed in a plastic cuvette (see page 425, column 2 and the attached Exhibit).

Column 1 on page 424 shows that the luciferase column catalyzes the reaction of luciferin to oxyluciferin with the generation of light. Importantly, there is no dNTPs in the luciferase column as these molecules have all been removed in the proceeding kinase columns. Any dNTPs in the luciferase column wherein a pressure field is used would interfere with the quanitation of the reaction. Unlike the present method recited in claim 1, Hyman does not teach or suggest applying an energy field to the sample, thereby separating said phosphate detectable moiety from said sample having an intact NP probe. When Hyman applies a pressure field, there is no intact NP probes present. Accordingly, Applicant respectfully request that the Examiner withdraw the rejection.

Moreover, Hyman does not anticipate claim 55. Claim 55 recites:

> 55. (Previously Presented) A method for sequencing a nucleic acid, said method comprising:
> providing a target nucleic acid, a polymerase priming moiety, a polymerase, and ***a plurality of intact NP probes***;
> mixing said target nucleic acid, said polymerase priming moiety, said polymerase and said plurality of NP probes under conditions permitting target dependent polymerization of said ***plurality of NP probes***, such conditions which are capable of providing a time sequence of a plurality of phosphate detectable moieties; and
> detecting over time ***said plurality of phosphate detectable moieties*** to provide a sequence of said target nucleic acid.

Hyman discusses at the bottom of page 424, column 1, bridging to column 2, "[a]fter a thorough column wash, buffer containing a different dNTP is introduced. Cycles of dNTP buffer followed by wash buffer are used in any desired deoxynucelotide order until the sequence is complete."

In no instance does Hyman teach or suggest a plurality of dNTPs in the sample to sequence the target nucleic acid. In claim 55, the sample contains all the NP probes necessary to sequence the target nucleic acid. In no instance using the method of Hyman can ***a time sequence of the phosphate detectable moieties be produced***, as is currently taught and claimed. In the method of claim 55, the phosphate detectable moieties are such that a time sequence of the phosphate detectable moieties can be produced. In the Hyman method, the light generated by the luciferase reaction is indistinguishable from each of the nucleotides used. Therefore, Hyman does not teach or suggest ***a time sequence of the phosphate detectable moieties being produced.*** As such, Applicant respectfully requests that the Examiner withdraw the anticipation rejection.

III. DOUBLE PATENTING

Claims 1-14, 16, 17 and 24-27 are free of the prior art, but remain rejected as allegedly being obvious over claims 22-36 of co-pending U.S. Patent application No. 09/876,374. In response, Applicant respectfully traverses the rejection.

Applicant believes that the present response places the application in condition for allowance. As such, under MPEP §804, when the Examiner is aware of two co-pending applications that would raise an issue of double-patenting if one of the applications became a patent, a "provisional" double patenting rejection should continue to be made by the Examiner in each application as long as there are conflicting claims in more than one application unless that "provisional" double patenting rejection is the only rejection remaining in one of the applications. If the "provisional" double patenting rejection in one application is the only rejection remaining in that application, the Examiner should then withdraw that rejection and permit the application to issue as a patent, thereby converting the "provisional" double patenting rejection in the other application(s) into a double patenting rejection at the time the one application issues as a patent.

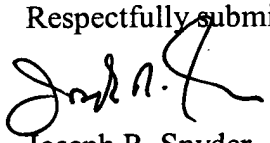
In view of the present response, the double patenting rejection is the only rejection remaining in the subject application, and U.S. Patent Application No. 09/876,374 is still pending. Therefore, Applicant respectfully requests that the Examiner withdraw this double-patenting rejection and allow the present application to issue.

IV. CONCLUSION

In view of the foregoing, Applicant believes all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



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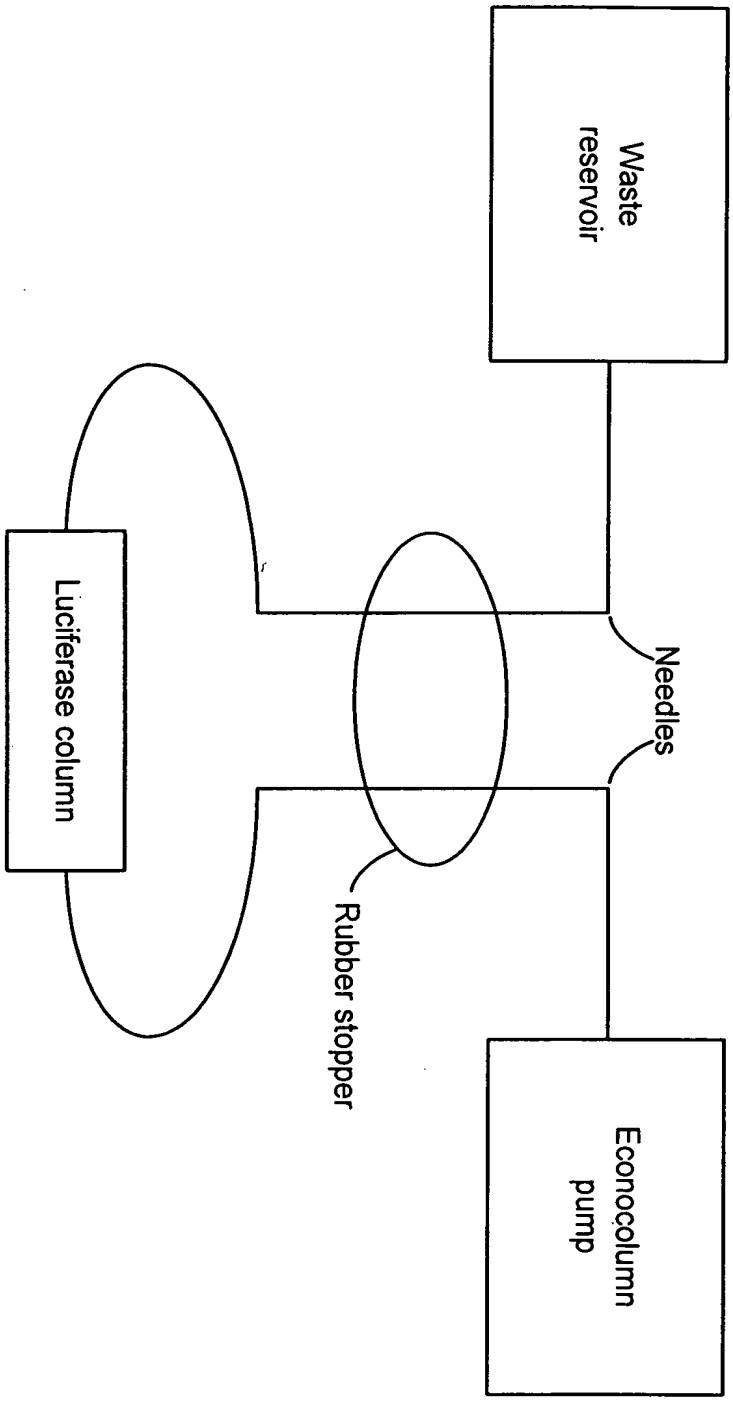

EXHIBIT